2009 Presidential Address: Beyond Darwin? Evolution, Coevolution, and the American Society of Human Genetics

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The following is Dr. McCabe's Presidential Address for the 59th American Society of Human Genetics Annual Meeting.

Introduction

Aloha and *Mahalo*! Thank you for electing me to be president of the American Society of Human Genetics (ASHG) during 2009. I am honored to serve you during this year and excited to preside over the 59th annual ASHG meeting in Hawai'i. I am convinced that the Program Committee and our ASHG staff have put together a meeting that fulfills the meeting tagline in an outstanding fashion: "Superlative Science, Sensational Setting."

In this year celebrating Darwin's contributions, I felt it was important for us to consider his impact, but also to consider if and how we may have moved beyond Darwin.

Darwin and Evolution

Charles Darwin lived from 1809 to 1882. Therefore, 2009 represents the 200th anniversary of Darwin's birth and the 150th anniversary of the publication of *On the Origin of Species by Means of Natural Selection*.[1] Evolution has gained increasing importance in human genetics and genetic medicine as a consequence of the Human Genome Project. Therefore, it is necessary to acknowledge this anniversary and to probe Darwin's contributions.

If we are to examine evolution, it is important to understand the etymology of this word. Originally used in 1622, evolution meant the "unrolling of a book," from the Latin *evolvere*, meaning *to unroll*.[2] The original use of evolution with the modern meaning was by the Scottish geologist Charles Lyell, in 1832. Interestingly, Darwin's use of the term in his 1859 *Origin of the Species* was limited to the final paragraph. His preferred terminology was "descent with modification," but "evolution" was eventually adopted and Darwin became closely identified with it.

Francisco Ayala, an evolutionary biologist, philosopher, and Darwin scholar, has argued that the Darwinian Revolution complemented the Copernican Revolution to complete the Scientific Revolution.[3] Just as "natural laws" were determined to govern the universe and redefined the structure of our solar system to be heliocentric, natural selection became a biological law of nature that explained biological diversity. We have referred to the Copernican Revolution in biology as a move away from a human-centered—an egocentric—view of biology to a more matrixed view in which humans are integral but not central parts.[4,5] We have argued that comparative genomics, which investigates the sequence documentation of natural selection and shows the incredible relatedness of free-living organisms, is important in this Copernican Revolution in biology.

Lessons learned from Darwinian evolution include the following: This process occurs by natural selection and involves adaptation to ecological pressures. We know that it is based upon genetic changes in the adapted organisms, and, as confirmed by comparative genomics, all free-living organisms are related evolutionarily and therefore genetically.

The Concept of Coevolution

Coevolution is defined as "evolution involving successive changes in two or more ecologically interdependent species (as of a plant and its pollinators) that affect their interactions."[6]

We can ask if Darwin, whose name is so closely tied to evolution, ever used the term coevolution. According to one source, this term was first used in 1964.[6] However, Paige sites as the first mathematical model of coevolution[7] a paper by Modes in 1958.[8] Therefore, since this term was first used in the latter half of the 20th century, the answer to the question is no; Darwin could not have used coevolution in his writing about evolution.

The next question is: Even if Darwin did not use the term coevolution, did he understand the concept? He used the term "coadaptation" in *On the Origin of Species* in the discussion of bees and flowers and the relationship between the physical structures of pollinators and flowers.[1] Therefore, Darwin did not use the term coevolution, but the answer to the question of whether he had the concept is yes.

Now, let us explore coevolution beyond biology to consider the coevolution of society and genetics. In the

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UCLA Center for Society and Genetics, we take the concept of coevolution as a central focus for our intellectual activities,[9] which was initially enunciated by the Center's codirector, Norton Wise.[10] In our consideration of coevolution of society and genetics among the members of the Center, the science does not shape society and society does not shape the science; they interact intimately and dynamically to shape each other. We would speculate that this view of coevolution would not have been accessible to Darwin.

Did Dogs Domesticate Humans?

While some may consider this controversial, there is evidence of a mutual domestication or coevolution of humans and wolves.[11,12] The archeological record does not show divergence of dogs and wolves until 14,000 to 15,000 years ago, but there is evidence that wolves and dogs began to diverge genetically from 40,000 to 100,000 or more years ago, and wolf bones are observed in proximity to human bones beginning more than 100,000 years ago.[11–17] One interpretation of these chronologic differences is that some wolves began to locate themselves around human camps at least 100,000 years ago, with mutual advantages accruing to both wolves and humans, and then beginning approximately 14,000 to 15,000 years ago humans had the time to select for desirable phenotypes, resulting in the observed differences in wolf and dog fossils.[11,12]

Comparative genomic analyses between wolves and dogs support this argument.[16] The gray wolf and dog are very close canid relatives with nuclear DNA coding sequences differing by approximately 0.04%. Their mitochondrial DNA diverged between greater than 100,000 and 15,000 years ago. The data indicate multiple origins and backcross admixture events. Ostrander and Wayne speculated that dogs and wolves may have had strong phenotypic similarity for a long period of time.[15] Therefore, the archeological record would not distinguish these canids until they began to phenotypically diverge beginning approximately 15,000 years ago. They speculated that this change in appearance might indicate "a change in the selection pressures associated with the transition from hunter gatherer to more sedentary lifestyles."

Grandin and Johnson quoted Australian Aborigines, who say "Dogs make us human," and added, "Now we know that's probably literally true."[12] They summarized the argument that dogs and humans coevolved. As dogs evolved from wolves, they changed genetically. Humans showed changes at approximately the same time that are similar to those seen in domesticated animals.

Groves noted that Fischer was the first to suggest that humans shared certain features with domesticated animals.[11] This concept of "self-domestication" was shared by others, including Lorenz in 1959 and Gould in 1977, but remained extremely controversial. One of the characteristics of domestication is a reduction in brain size. This has happened with humans and is most remarkable for the olfactory bulbs, which are 29% and 27% in relative proportion to gorilla and chimpanzee, respectively. Groves hypothesized that the relationship between humans and dogs was symbiotic and long. Dogs provided to humans warning of intruders, assistance with tracking and hunting, disposal of garbage, companions for children in the form of protection and play, and warmth in the cold. In return, humans provided to dogs a secure source of nutrition and protection from predators. Groves concluded, "The relationship was stable over 100,000 years or so, and intensified in the Halocene into mutual domestication. Humans domesticated dogs, and dogs domesticated humans."

Questions remain about the process of domestication. Wildlife and behavioral ecologists speculate that some wolves adapted to being around bands of humans from whom they could scavenge, and therefore [humans] provided the wolves with a ready food source.[18] Those wolves with less fear of and a bolder disposition toward humans did well. Eventually these bolder wolves separated from their more cautious wolf relatives.

This long process of coevolution and codomestication has had significant behavioral consequences. Let's compare the social cognitive skills of nonhuman primates and dogs.[19] Nonhuman primates are able to follow the gaze of humans to identify the location of food. Chimpanzees can do this in the face of visual distractions and sight barriers. They are considered to have a fair degree of sophistication regarding visual cognition of those with whom they are interacting. But, in finding food hidden from vision in containers, dogs show greater social cognitive skills than chimpanzees, for example following the directions from humans provided by pointing, gazing, or marking (e.g., with a wooden block). Dogs performed better than wolves in gaze-point-tap and point only. Puppies were tested, and gaze-point and gaze only were both above chance, and no difference was observed based on age. Kennel-reared dogs were compared with family-reared, and there was no difference between these groups. These investigators concluded that the excellent social cognitive skills of dogs were positively selected in the process of domestication. They speculated dogs that were more capable of reading the social cues to predict human behavior had a "selective advantage." The social cognitive interactions between humans and dogs coevolved during the process of mutual domestication.

There are many other examples of coevolution, one of which involved humans, cattle, the dairy culture, and lactose tolerance.[5] Lactase persistence penetrated human genetics extremely rapidly, and the genetic diversity of the cows' milk proteins correlated geographically with the degree of lactase persistence in Europe. New information from bovine genomics has increased the richness of our understanding of their coevolution with humans. The genomic sequencing of taurine cattle shows increased variation in the genes involved not only for lactation, but also for immune defense, the latter representing important

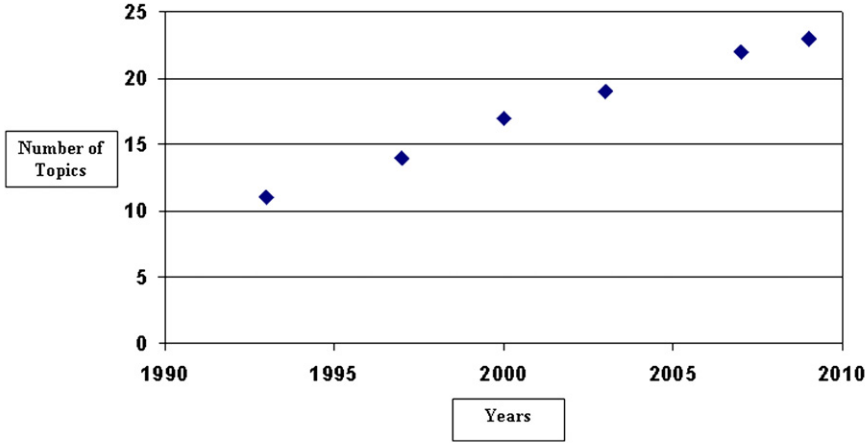

Figure 1. ASHG Annual Meeting Topics, 1993–2009
Data provided by J. Boughman, Ph.D., ASHG Executive Vice President.

adaptations for bacterial fermentation in the rumen and herd husbandry with increased risk of disease.[20] The genetic structure among cattle breeds shows decreased population size compared with the ancestral population.[21] More aurochs (extinct ancestors of European domestic cattle, *Bos taurus*) were domesticated than wolves, and cattle tolerated bottlenecks better.

There are important lessons to be learned from domestication. The traditional narrative of domestication argues humans determined the traits of domestic animals. This is a humancentric and deterministic view. The coevolutionary narrative maintains that humans and animals coevolved genetically in the process of domestication. This nondeterministic view recognizes the Copernican Revolution in biology.

Coevolution of Genetics and ASHG

Genetics and ASHG are constantly changing. For these changes to be positive, they must be dynamically coevolving and not changing in isolation from each other. I will argue that genetics and ASHG are coevolving, but we must be aware that changes in genetics could threaten the focus of ASHG.

As evidence that genetics is constantly changing, let's consider disciplines that have developed and been incorporated into the ASHG community. These include cytogenetics, biochemical genetics, molecular genetics, genomics, transcriptomics, proteomics, and systems biology.

These additions to the ASHG community have created a challenge for the annual meetings' Program Committees, causing difficulties in keeping up with the changes in the science. For example, they have been required to generate new topics, and these slightly more than doubled, from 11 in 1993 to 23 in 2009, with an approximately linear increase in the topics over these 17 years (Figure 1).

There may be problems with the expansion of the breadth of the science associated with our Society. We must recognize and maintain ASHG's focus. We cannot and should not try to include all of biomedical science in our meetings. This may become an even greater challenge as genetics becomes so important in biomedical research and clinical practice.

Let us look to the ASHG vision statement[22] to see if it provides any guidance:

> Members of ASHG enter the 21st century with a commitment to become fluent in the language of the genome, understand human variation, and promote the public health. As we transfer new knowledge to the next generation of genetics professionals and the public, we will translate new ideas into improved clinical practice.

This vision statement does provide suggestions to limit the breadth of The Society's interests, but does ASHG provide guidance to the implementation of The Society's vision?

For guidance about implementation, let us look to our tagline: "*discover* • *educate* • *advocate*." ASHG provides opportunities to discuss research in human genetics and its translation into clinical practice at our annual meetings and in our publications, including in print in *The American Journal of Human Genetics* and online in SNP-IT. We can merge the ASHG's vision and tagline to provide an implementation of our focus in the areas of genetics and genomics:

- *Discover*—We assist our members to become able in the most current science and to understand human variation.
- *Educate*—We transfer new knowledge to the next generation of genetics professionals and the public.
- *Advocate*—We promote the public's health.

ASHG provides a forum to present new knowledge in genetics and genomics, and we will translate these new ideas into improved clinical practice.

Our focus is in our vision statement, and our tagline tells us how to implement that vision. Those who created our vision statement and tagline provided us with the guidance needed to maintain our focus, and yet allow us to grow dynamically with new knowledge in our discipline.

Coevolution of ASHG and the Genetics Community

ASHG and you, our membership, are coevolving with the broader genetics community in an intimate and dynamic fashion. To address focused issues in this coevolution, we are pursuing two initiatives: the first on international human genetics, and the second on corporate responsibility specifically related to microarray analytical algorithms.

The rationale for the international initiative is as follows. If we believe basic research translates into improved clinical care, and an active local and/or regional genetics community improves local care and public health, then it is incumbent upon the ASHG to collaborate to build the human genetics research and translational infrastructure internationally. To implement this initiative, we have developed an International Task Force. This continues efforts initiated and continued by previous presidents. The International Task Force includes international and North American members. Its purpose is to identify strategic opportunities to actively engage our entire membership, to develop new knowledge in an internationally collaborative manner, and to translate that new knowledge to promote the public health and to improve clinical practice. We need to be sure to include the countries in which the largest population growth is anticipated over the next 40-50 years, since these countries—China and India—are expected to have the largest numbers of children and adults with genetic diseases.[23]

The rationale for the corporate responsibility initiative is as follows: When I entered biomedical research in 1961, and through much of my career, we knew if the experiment had worked by looking at the color changes in the tubes. We only put the solutions in a spectrophotometer to quantify the data. With the advent of microarrays, however, we cannot see the results, and we are buffered even more from the data by analytical algorithms that are used to interpret the microarray data. Therefore, we must *trust* the hardware and software manufacturers. Currently this impacts our research results, but as this technology is translated into the clinical arena, the algorithms will impact clinical decision making.

This interest in corporate responsibility in microarray algorithms stemmed from an experience we had with an abstract we presented at the 2008 ASHG Annual Meeting, describing expression microarray data comparing wild-type and glycerol kinase knockout mice. When the first author on the abstract, Nicole Henderson-MacLennan, reran the data with the same proprietary algorithm prior to preparing her poster, she found very different results. The company had changed the algorithm and there were problems with the new version. Even more concerning was that the company knew there was a problem. Their response to our concern was that if investigators identified the software version in the methods section of their presentations or publications, then it would be understood if others could not reproduce the results. Up to the time of this presentation, the company has yet to inform its users of the problem. As we have investigated this problem, we have found that it is a more general concern (E.R.B.M., unpublished data).

The Corporate Responsibility Task Force includes members from the corporate and academic sectors. Its goals are to identify challenges in the integration of hardware and software manufacturing, to develop points to consider in this focused area of corporate responsibility, and to determine if there are other areas to address regarding corporate responsibility.

Beyond Darwin?

Darwin clearly understood the biological concepts of evolution and coevolution, and he proposed the interacting influences of three core elements: natural selection, variation, and heredity.[24] The word symbiosis, however, was not coined until 1877.[25] Competition is critical to many interpretations of Darwinism, and symbiosis and cooperation bring new dimensions to concepts of evolution and coevolution.[24,26] Concepts within evolution and coevolution have, themselves, evolved since Darwin. It is unclear that he would recognize the cooperative concepts of symbiosis or coevolution. It is likely that Darwin's lack of understanding would be particularly acute as we discuss the coevolution of science and society; for example, in the UCLA Center for Society and Genetics.[9]

Darwin's influence on biological thinking has been incredible, and it is important that we celebrate Darwin and his ideas. But, have we moved beyond Darwin? The answer is an emphatic yes! Conceptually, our ideas continue to evolve, coevolve, and move forward. It is essential for the ASHG to coevolve with the scientific and social contexts of human genetics as we "*discover* • *educate* • *advocate*."

Conclusion

The 59th annual meeting of the ASHG in Honolulu, Hawai'i, brings you "Superlative Science, Sensational Setting." Again, please accept my sincerest *Aloha* and *Mahalo*. Thank you so very much for allowing me to serve as your president during 2009 and for honoring me in this manner!

References

1. Darwin, C. (1859). On the Origin of Species by Means of Natural Selection (London: John Murray).
2. Evolve. Online Etymology Dictionary. Retrieved December 30, 2009, from Dictionary.com website: http://dictionary.reference.com/browse/evolve.
3. Ayala, F.J. (2007). Darwin's greatest discovery: design without designer. Proc. Natl. Acad. Sci. USA *104* (Suppl 1), 8567–8573.
4. McCabe, E.R.B. (2001). Clinical genetics: compassion, access, science, and advocacy. Genet. Med. *3*, 426–429.
5. McCabe, L.L., and McCabe, E.R.B. (2008). DNA: Promise and Peril (Berkeley, CA: University of California Press), pp. 55–67, 69–72.
6. Coevolution. Merriam-Webster OnLine. Retrieved January 5, 2010: http://www.merriam-webster.com/dictionary/coevolution.
7. Paige, K.N. (1958). Coevolution. Lecture slides. Retrieved January 5, 2010: http://www.life.illinois.edu/ib/443/lectures/EVOLCOEVOL.PPT#265,1,COEVOLUTION.

8. Modes, C.J. (1958). A mathematical model for the co-evolution of obligate parasites and their hosts. Evolution *12*, 158–165.
9. UCLA Center for Society and Genetics. Vison – coevolution. Retrieved January 9, 2010: http://www.socgen.ucla.edu/Vision.html.
10. Wise, N. UCLA Department of History. Retrieved January 9, 2010: http://www.history.ucla.edu/people/faculty?lid=747.
11. Groves, C.P. (1999). The advantages and disadvantages of being domesticated. Persp. Hum. Biol. *4*, 1–12.
12. Grandin, T., and Johnson, C. (2005). Animals in Translation: Using the Mysteries of Autism to Decode Animal Behavior (New York: Scribner), pp. 176–177, 303–307.
13. Vilà, C., Savolainen, P., Maldonado, J.E., Amorim, I.R., Rice, J.E., Honeycutt, R.L., Crandall, K.A., Lundeberg, J., and Wayne, R.K. (1997). Multiple and ancient origins of the domestic dog. Science *276*, 1687–1689.
14. Lindblad-Toh, K., Wade, C.M., Mikkelsen, T.S., Karlsson, E.K., Jaffe, D.B., Kamal, M., Clamp, M., Chang, J.L., Kulbokas, E.J. 3rd, Zody, M.C., et al. (2005). Genome sequence, comparative analysis and haplotype structure of the domestic dog. Nature *438*, 803–819.
15. Ostrander, E.A., and Wayne, R.K. (2005). The canine genome. Genome Rev. *15*, 1706–1716.
16. Wayne, R.K., and Ostrander, E.A. (2007). Lessons learned from the dog genome. Trends Genet. *23*, 557–567.
17. Gray, M.M., Granka, J.M., Bustamante, C.D., Sutter, N.B., Boyko, A.R., Zhu, L., Ostrander, E.A., and Wayne, R.K. (2009). Linkage disequilibrium and demographic history of wild and domestic canids. Genetics *181*, 1493–1505.
18. Pennisi, E. (2002). Canine evolution. A shaggy dog history. Science *298*, 1540–1542.
19. Hare, B., Brown, M., Williamson, C., and Tomasello, M. (2002). The domestication of social cognition in dogs. Science *298*, 1634–1636.
20. Elsik, C.G., Tellam, R.L., Worley, K.C., Gibbs, R.A., Muzny, D.M., Weinstock, G.M., Adelson, D.L., Eichler, E.E., Elnitski, L., Guigó, R., et al. Bovine Genome Sequencing and Analysis Consortium. (2009). The genome sequence of taurine cattle: a window to ruminant biology and evolution. Science *324*, 522–528.
21. Gibbs, R.A., Taylor, J.F., Van Tassell, C.P., Barendse, W., Eversole, K.A., Gill, C.A., Green, R.D., Hamernik, D.L., Kappes, S.M., Lien, S., et al. Bovine HapMap Consortium. (2009). Genome-wide survey of SNP variation uncovers the genetic structure of cattle breeds. Science *324*, 528–532.
22. Vision Statement, A.S.H.G. Retrieved January 31, 2010: http://www.ashg.org/pages/about_mission.shtml.
23. McCabe, E.R.B. (2007). American Pediatric Society presidential address 2007: Robust complex networks in health, disease and international pediatric research. Pediatr. Res. *62*, 374–379.
24. Speidel, M. (2000). The parasitic host: symbiosis *contra* neo-Darwinism. Pli *9*, 119–138.
25. Sapp, J. (1994). Evolution by Association: A History of Symbiosis (New York: Oxford University Press), pp. 6–7.
26. Ryan, F. (2002). Darwin's Blind Spot: Evolution Beyond Natural Selection. (New York: Houghton Mifflin Company). pp. 1–7, 15–24, 47–53, 239–268.